REMARKS

Applicant has amended claim 1 to delete the recitation that P_1 and P_2 may be the same. Applicant has added claim 46, which depends from claim 1, and which is supported at paragraph [0051]. Accordingly, Applicants submit that no new matter has been added. Entry of the amendment is respectfully requested.

Claims 1-19 and 27-28 have been rejected under 35 U.S.C. §103(a) as being unpatentable over *Lipton* (United States Patent 5,028,592) in view of *Kauvar* (United States Patent 5,786,336). The Patent Office has determined that "[i]t would have been obvious to one of ordinary skill in the art to synthesize the KPV tripeptide in its diamide form in the diacetyl KPV tripeptide synthesis methods of *Lipton* because *Kauvar* advantageously teach[es] [that] in the peptide arts it was known that the diamide form of tripeptide synthesis allows for such tripeptides to optimally exert intracellular effects." Office Action, pages 3-4. Applicant respectfully traverses the rejection.

Lipton is directed to a lysine-proline-valine ("KPV") tripeptide for the treatment of inflammation. *Lipton* provides a single synthetic method of preparing a KPV tripeptide, which involves preparing protected intermediates and purification of the tripeptide on a silica gel column. *Lipton*, col.7, ll.45-67 to col.8, ll.1-62. This method is a solution phase synthesis that follows the general procedures of earlier KPV synthetic methods. *Application*, ¶¶ [0008] - [0012]. As conceded by the Examiner, *Lipton* does not teach KPV tripeptide <u>diamides</u>. Office Action, page 3.

Kauvar is directed to a method of improving the effect of a chemotherapeutic by administering glutathione analogs. *Kauvar*, col.1, ll. 15-22. *Kauvar* also teaches enhanced intracellular effects through glutathione diesters or diamides. *Kauvar*,

col.2, ll.37-40. As conceded by the Examiner, *Kauvar* does not disclose KPV tripetides or their method of synthesis, let alone KPV tripeptide diamides. Office Action, page 3.

Applicant disagrees with the Office's contention with respect to there being only one difference between the cited art and the claimed invention.

The claimed method of KPV tripeptide synthesis entails formation of a lysine-proline dipeptide ("KP dipeptide") intermediate. The amine groups of the lysine residue are protected, thus allowing for further derivation. *Lipton* teaches a lysine residue wherein both amine groups are protected with the same benzyloxycarbonyl protecting group. There is no teaching or suggestion that different protecting groups could be used. In the claimed invention, on the other hand, each amine is protected with a different group, allowing regioselective protection and/or deprotection, which is important in subsequent coupling steps. For example, the P_1 protecting group may be removed under reaction conditions which do not affect the P_2 protecting group, allowing further reaction at the α-NH_2, but not at the ϵ-NH_2 of the lysine residue. Such regioselective deprotection and subsequent derivation cannot be achieved in *Lipton*.

Following formation of the dipeptide, the claimed method entails coupling of the KP-dipeptide intermediate with a valine residue. In *Lipton*, a valine ester is reacted, while in the claimed invention a valine amide is reacted, providing the first of two amide groups on the KPV tripeptide. *Lipton* does not teach or suggest using valine residues containing substituents other than an ester group, and, as a result, does not teach tripeptide diamides or even monoamides.

The claimed invention further entails amidifying the α-NH_2 group with a moiety other than a protecting group following regioselective deprotection. This step introduces a second

amide group, which, as the Examiner concedes, *Lipton* does not teach or suggest. Office Action, page 3.

New claim 46 distinguishes the claimed invention even further in that it expressly disclaims any final purification step. *Lipton*, on the other hand, requires chromatographic purification on a silica gel column. *Lipton*, col.8, ll.36-40.

One skilled in the art would not have been motivated by the teachings of *Kauvar* to modify the synthesis of *Lipton*. *Kauvar* does not relate at all to KPV tripeptide diamides and instead teaches only glutathione analogs, which are structurally and functionally unrelated compounds. Nor does *Kauvar* suggest that methods of making glutathione analogs could be applied to the synthesis of the structurally and functionally distinct KPV tripeptides.

Moreover, it appears that *Kauvar* regards diester and diamide glutathione analogs as equivalents, given that each exert enhanced intracellular effects. *Kauvar*, col.2, ll.37-40. As such, even if one skilled in the art would have been motivated to modify *Lipton's* method in the manner alleged by the Office, given that *Lipton* uses a valine ester in its KPV synthesis, one skilled in the art would have simply added a second ester group, as opposed to a valine amide, to achieve enhanced intracellular effects. Applicant submit that the claimed invention would not have been obvious over the collective teachings of the cited references.

Aside from the foregoing, there is nothing in the collective teachings of the cited art which suggest that the claimed method would have resulted in a higher yield of KPV tripeptide. As shown in the working examples, embodiments of the claimed invention achieved yields which were more than double the yield achieved using *Lipton's* method. *Application*, ¶¶ [0119] to [0127]; see also [0009] and [0010] for prior art yield. Indeed, it has been shown by the Applicant "that [with]

an appropriate selection of the protective groups, the reagents to be used and the reaction sequence makes it possible to increase the yield, in a solution synthesis, from 33% to more than 70%." *Application*, ¶¶ [0052] and [0053].

In view of the foregoing, reconsideration and withdrawal of the rejection are respectfully requested.

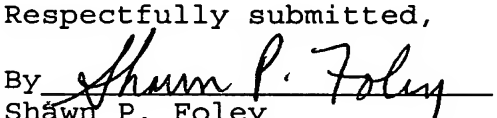
As it is believed that all of the rejections set forth in the Official Action have been fully met, favorable reconsideration and allowance are earnestly solicited.

If, however, for any reason the Examiner does not believe that such action can be taken at this time, it is respectfully requested that he/she telephone applicant's attorney at (908) 654-5000 in order to overcome any additional objections which he might have.

If there are any additional charges in connection with this requested amendment, the Examiner is authorized to charge Deposit Account No. 12-1095 therefor.

Dated: September 24, 2007

Respectfully submitted,

By 

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